UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,001	02/22/2002	Hans-Ulrich Demuth	20784/6	1724

7590 08/11/2004

Brown Rudnick Berlack Israels, L.L.P.
One Financial Center
Boston, MA 02111

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,001	DEMUTH ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *11-13 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-25 are pending.

Applicants' amendment filed May 24, 2004 is acknowledged. Applicants' response has been fully considered. Claim 14 has been amended, and claims 11-13 and 23-25 are non-elected invention and withdrawn from consideration. Thus, claims 1-10 and 14-22 are examined.

Oath/Declaration

2. A newly submitted oath filed May 24, 2004 is acknowledged.

Objection Withdrawn

3. The previous objection of claim 14 is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 6 in the amendment filed May 24, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 102

4. The previous rejection of claims 1-4, 7, 9, 10, 14-17, 20 and 22 under 35 U.S.C. 102(e) as anticipated by Kohn *et al.* (U. S. Patent 6,517,824, Filed may 20, 1996), is withdrawn in view of applicants' response at pages 10-11 in the amendment filed May 24, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10 and 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of general formula B-A-C having the inhibitory activity against DP-IV, and a pharmaceutical composition comprising the compound; or a compound of amino acid pyrrolidide, cyanopyrrolidide or 4-hydroxyproline with amino acid side chain blocked and having the inhibition against DP-IV, or a pharmaceutical composition comprising the compound as indicated in the prior art, does not reasonably provide enablement for a compound of the general formula, B-A-C or a pharmaceutical composition comprising the compound, where the structure or the function of the compound is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-10 and 14-22 are directed to a compound of the general formula, B-A-C (claims 1-8) or a pharmaceutical composition (claims 9, 10 and 14-22) comprising the compound, where A is an amino acid having a functional group, B is an oligopeptide, PEG or an organic group having 8-50 carbon atoms, and C is thiazoline, pyrrolidine, cyanopyrrolidine, hydroxyproline, dehydroproline and piperidine. The specification indicates the present invention provides a compound having a general formula, B-A-C, which can locally inhibit DP-IV activity (pages 4-6). There are no indicia that the present application enables the full scope of the claims in view of the compound having a general formula, B-A-C but without a defined function and a pharmaceutical composition comprising the compound as discussed in the stated rejection. The present application

does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the compounds of formula B-A-C without a defined structure or function; and a pharmaceutical composition comprising the compound, where the function of the compounds and their use in the treatment are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification indicates the preparation of specific glutamylthiazoline such as Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, and their inhibitory activities toward DP-IV (Examples 1-3). The data indicate side-chain modified compounds inhibit plasma-DP-IV more slowly as compared to unmodified inhibitors, and in the case of Glu-$(Gly)_5$-Thia, no systemic action of the orally administered active ingredient is detectable, thus it is suggested these compounds may be used as basic structures for synthesizing topically administrable DP-IV inhibitors without systemic action. However, there are no working examples indicating various functions or activities of the claimed variants other than as DP-IV inhibitors for topical use.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Jenkins *et al.*, WO-95/15309; Ashworth *et al.*, Bioorg. Med. Chem. Lett. 6, 1163-1166 (1996)) teaches the amino acid pyrrolidide, cyanopyrrolidide or 4-hydroxyproline having certain amino acid side chain (e.g., Lys, Thr, Orn, Glu or Ser) blocked with PEG or other organic groups as inhibitors of DP-IV and the K_I values against DP-IV *in vitro*. However, the prior art does not disclose a compound of formula B-A-C with an undefined structure or function, nor indicates the use of the compound in areas other than as DP-IV inhibitors. Thus, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the function or activity of compounds with the formula of B-A-C, and their use in areas other than inhibiting DP-IV or treating disorders which are not DP-IV related conditions to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass numerous compounds of the formula of B-A-C with an undefined structure or function, and a pharmaceutical composition comprising the compound. While the specification shows a specific example of an amino acid side modified compound of B-A-C (i.e., Glu(Gly_3)-Thia, Glu(Gly_5)-Thia and Glu(PEG)-Thia) inhibits plasma DP-IV quite slowly (Table 1), and Glu(Gly_5)-Thia does not show any systemic action of the orally administered compound, the specification does not demonstrate various functions or activities of B-A-C compounds and their use in the areas other than inhibiting DP-IV. Since the specification does not provide sufficient teachings in structures or functions of various compounds of B-A-C, the effects of the compounds in the treatment are not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to amino acid side chain modified compounds of B-A-C or a pharmaceutical composition comprising the compound. While the specification indicates a compound having a general formula, B-A-C can locally inhibit DP-IV activity, and Examples 1-3 demonstrate glutamylthiazoline such as Glu(Gly_3)-Thia, Glu(Gly_5)-Thia or Glu(PEG)-Thia, which inhibits DP-IV potently with equal low values of K_I *in vitro*, inhibits plasma DP-IV quite slowly in rat model (Table 1); and Example 2 further indicates these side chain-modified DP-IV inhibitors may consequently act as basic structures for synthesis of novel topically administered DP-IV inhibitors without systemic action, the specification does not demonstrate various functions or activities of compounds of B-A-C other than inhibiting DP-IV, nor their use in the treatment of disorders which are not DP-IV related conditions. Moreover, there are no working examples indicating various functions/activities or use of the claimed variants. Since the specification has not provided sufficient teachings on the structure or function of compounds of B-A-C, it is necessary to have additional guidance and to carry out further experimentation to assess the functions/activities of various compounds of B-A-C and their use in the treatment of various conditions.

(6). Nature of the Invention

The scope of the claims includes many variants of side chain-modified compounds of B-A-C and a pharmaceutical composition comprising the compound, however, the specification has not demonstrated various functions or activities of these

variants, and their use in the treatment of various conditions. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the effects of the compound is unpredictable and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the activities of various compounds of B-A-C and their use in the treatment.

In response, applicants indicate the Examiner references neither the level of knowledge of "one of ordinary skill in the art," nor the nature of the impediments to enablement one might encounter; the specification clearly disclose that the goal of the invention is to decrease or prevent a systemic distribution of the DP IV inhibitors of the present invention by means of voluminous hydrophilic substitutions on the side chain of DP IV inhibitors, resulting in DP IV-inhibitors of the formula B-A-C, and preferred structures of these hydrophilic side chains are disclosed; Example 1 and table 1 prove that the transportability of the side-chain-modified DP IV-inhibitors according to the present invention is dramatically diminished, thus these DP IV-inhibitors are therefore excellently suited to achieving locally limited (topical) inhibition of DP IV in the body; and the utility of a chemical compound for a particular disease state may be confirmed by establishing that it possesses properties of therapeutic value through the aforementioned tests conducted on standard experimental animals, and the specification has disclosed examples and data on standardized laboratory animals, which can clearly be used by one skilled in the art to understand therapeutic utility. Thus, no undue experimentation is required to confirm the possession of such therapeutic effectiveness.

The response has been considered, however, the argument is not found persuasive because of the following reasons: The specification only demonstrates a specific example of an amino acid side modified compound of B-A-C (i.e., Glu(Gly_3)-Thia, Glu(Gly_5)-Thia and Glu(PEG)-Thia) as a DP-IV inhibitor, which can be administered topically because of its decrease in systemic distribution (Examples 1-2, table 1), however, the specification does not demonstrate the effects of various compounds of B-A-C with an undefined structure (i.e., A being any amino acid with a functional group and B being oligopeptide having up to 20 amino acids or an optionally substituted organic group) or undefined function (inhibiting DP-IV is not indicated) and their use in the treatment, which are encompassed by the claims. Although the tests conducted on compounds as DP-IV inhibitors and standard experimental animals can be performed in view of the knowledge in the art, the claims encompass numerous compounds of B-A-C where the structures or functions are not sufficiently disclosed. Furthermore, the specification does not provide sufficient teachings on the functions or activities of various compounds of B-A-C and their use in the treatment as indicated in the analysis of Wands factors. Therefore, it is necessary to have additional guidance on the functions or activities of the compounds and carry out undue experimentation to assess the effects of these compounds in the treatment of various conditions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 14-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the limitation "when A is selected from (c)" in lines 17-18. There is insufficient antecedent basis for this limitation in the claim because "A" is defined as an amino acid having at least one functional group in the side chain in line 6. Claims 14-22 are indefinite because of the use of the term "may not be". The term cited renders the claim indefinite, it is unclear whether the limitation following the term is part of the claimed invention because the term "may not be" indicates group C is not pyrrolidine or cyanopyrrolidine in one possibility, or, group C can be pyrrolidine or cyanopyrrolidine in another possibility. Claim 14 also recites the limitation "the site of action" in line 18. There is insufficient antecedent basis for this limitation in the claim, and it is also not clear what is the site of action, and how does it affect the pharmaceutically acceptable material. Claims 15-22 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicates claim 14 has been amended, thus the rejection has been overcome. The response has been considered, however, the argument is not found persuasive because the added term "when A is selected from (c), C may not be pyrrolidine or cyanopyrrolidine " in lines 17-18 does not resolve the issue of indefiniteness as indicated in the section above, although the claim has been amended. Please note the word "pyrrolidide" remains in the claim, see line 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 14-17, 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Jenkins *et al.* (WO-95/15309).

Jenkins *et al.* disclose various dipeptidyl peptidase IV (DP-IV) inhibitors such as Glu($NH(CH_2)_5COOBn$) pyrrolidide (compound 59 in Table 3) and Glu($NH(CH_2)_5COOBn$) cyanopyrrolidide (compound 97 in Table 3), where the side chain of Glu is covalently linked to a $NH(CH_2)_5COOBn$, which is a substituted amine having 12 carbon atoms; and the inhibitors were tested in Hepes pH 7.8 buffer solution (a pharmaceutically acceptable adjuvant) for their inhibition against DP-IV (pages 9-10; Table 9; claims 14-17, 21 and 22).

In response, applicants indicate claim 14 has been amended, thus claim 14 and other rejected dependent claims are not longer anticipated by Jenkins *et al.* The response has been considered, however, the argument is not found persuasive because the added limitation does not exclude the compounds of Jenkins *et al.* due to insufficient antecedent basis and indefiniteness of the added term.

8. Claims 14-17, 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Ashworth *et al.* (Bioorg. Med. Chem. Lett. 6, 1163-1166 (1996)).

Ashworth *et al.* disclose a series of DP-IV inhibitors such as Lys(Z)-cyanopyrrolidide (compound 28 in Table II), where the side chain of Lys is covalently

linked to Z group ($C_6H_5CH_2OCO$-), which is a substituted aromatic compound having 8 carbon atoms; and the inhibitors were tested in pH 7.4 buffer solution (a pharmaceutically acceptable adjuvant) for their inhibition against DP-IV (Table II, page 1166; claims 14-17, 21 and 22).

In response, applicants indicate claim 14 has been amended, thus claim 14 and other rejected dependent claims from are not longer anticipated by Ashworth *et al.* The response has been considered, however, the argument is not found persuasive because the added limitation does not exclude the compounds of Ashworth *et al.* due to insufficient antecedent basis and indefiniteness of the added term.

Conclusion

9. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
July 31, 2004

Jon P. Weber, Ph.D.
Primary Examiner